Further, based on the amendments above, all claims depend either directly or indirectly on claim 4 and are sufficiently related that it would not cause the Examiner to incur an undue burden to analyze them together. Consequently, Applicants submit that any restriction requirement based on the claims as amended would be inappropriate.

In addition to asserting a restriction requirement, the Examiner rejects all of the pending claims under 35 U.S.C. §§ 102 and 112. The Examiner also objects to certain portions of the Specification. Based on the amendments above and the arguments below, Applicants respectfully submit that all outstanding rejections and objections should be withdrawn.

Summary of the Invention

Applicants' invention relates to the field of nucleic acid sequence analysis. Specifically, the invention provides methods of nucleic acid sequence analysis that use combinatorial sequence array primers to sequence and/or to detect mutations or polymorphisms within a template nucleic acid. Sequencing and/or detection are accomplished by determining a region of complementarity through the use of a sequencing reagent that contains a primer and extending that primer in order to determine whether there was complementarity.

Amendments and New Claims

Claim 4, subsection (c) has been amended to make explicit what was implicit -- that the spacer does not form a duplex with the target. The spacer will not be able to form a duplex either because it comprises a sequence of nucleotides that are not complementary to the target region adjacent to the region to which the primer is complementary, or the spacer comprises moieties that are not nucleic acids and thus cannot form duplexes with any nucleotide sequences. Support for this amendment is, for example, found in Figure 2 in light of the portion of the Specification previously cited to the Examiner. See pages 15 -16 of the Specification. Applicants have also amended claim 4, subsection (d) to provide that the primer needs to be extended by one or more nucleotide moieties. Support for this amendment may, for example, be found on page 24, lines 10 -12.

Claims 19, 23 and 27 have been amended so that they depend on claim 4. Claim 20 has been amended in a manner consistent with claims 4 and 19 to ensure that there is proper antecedent basis.

New claim 35 is directed to a process that uses a plurality of reagents in connection with an array. Support for this amendment may, for example, be found on page 31, lines 26 - 31. No new matter has been added.

New claim 36 is directed to species in which the spacer comprises one of a select group of non-nucleotide moieties. Support for this claim may, for example, be found on page 15 of the Specification.

Response to Rejection of Claims 4 -18 and 28 under 35 U.S.C. § 112, ¶1

The Examiner rejects claims 4 -18 and 28 as containing subject matter that was not described in the Specification in such a way as to convey to one skilled in the art that the inventors, at the time that the application was filed, had possession of the claimed invention. Specifically, the Examiner asserts that the pages that Applicants cited for support do not support the limitation of part (c) of the amended claim that is directed to the spacer's complementarity. Applicants respectfully disagree and point to additional parts of the Specification that support this limitation.

Part (c) of currently pending claim 4 provides a step in which there is "scanning the captured template using said primer-polymerase complex for a region of complementarity to said primer region and forming a duplex, wherein said region of complementarity to said primer region is not adjacent to a region that is capable of forming a duplex with said spacer region." In this step, the reagent has the ability to form a duplex with one or more regions of the template that have sequences that are complementary to the primer sequence after the template has been captured. The specificity of the primer region is defined by its sequence, which enables it to form a duplex with complementary sequences on the target.

By contrast, the spacer, by either being a sequence that is not complementary to the region adjacent to the region to which the primer is complementary or being a moiety other

than a nucleotide sequence imparts flexibility. As the Specification emphasizes, the "template-reagent complex is incubated under conditions which allow duplex formation between the primer sequence of the sequence reagent and sequences of the template nucleic acid molecule that are complementary to the primer sequence." Specification page 27, lines 23 –27 (emphasis added). It permits the reagent to form duplexes to multiple regions to which the primer is complementary. If by contrast the spacer were to be complementary to the region adjacent to the sequence that is complementary to the primer, the reagent would prefer aligning to a region in which both the spacer and the primer were complementary.

Applicants respectfully submit that the application evidences the possession of this invention and in addition to the sections to which Applicants previously pointed the Examiner, point the Examiner to Figure 2. Figure 2a shows a capture step. Figure 2b shows a scanning step. In Figure 2b, as the primer scans the template, the spacer region does not align with the template, which demonstrates that in the process described in that figure, it is not complemetary and does not form a duplex product with any region of the template. If it were to form such a product, the primer region would not scan the template as effectively, because the primer would preferentially align immediately downstream of where the spacer aligned. See also page 24, lines 1 -19 (primer region of reagent may form duplex with sequences of target).

Moreover, that the spacer region is contemplated as being species that are not complementary to the region adjacent to the region that is complementary to the primer region is evidenced by the inclusion in the Specification of moieties such as polyethylene glycol, 5-nitro-indole groups and random, non-random and pseudo-random bases. See Specification page 15, lines 23 -33.

Based on the foregoing, Applicants respectfully request that this rejection be withdrawn and that claim 4 and the claims that depend on it be allowed.

Response to Rejection of Claim 31 under 35 U.S.C. § 112, ¶1

The Examiner also asserts that the Specification does not contain a written description sufficient to support the limitation of mass spectrometry in claim 31. As the Examiner notes,

the disclosure does provide that MADI-TOF mass spectrometry may be used in connection with the present invention. Applicants respectfully submit that a species can provide written description support for a genus and that a person skilled in the art would recognize that at the time of file this application, the inventors appreciated that their invention was not limited to the application of one type of mass spectrometry. Further, the Examiner has not indicated that there are any differences in the application of different types of mass spectrometry that would make some but not other applications useful with the present invention. Thus, Applicants respectfully request that this rejection be withdrawn.

Response to Rejection of Claim 32 under 35 U.S.C. § 112, ¶1

The Examiner rejects claim 32, asserting that the Specification does not provide an adequate written description for this claim. The Examiner asserts that the portions of the Specification to which Applicants directed the Examiner reveal repeating the method for each sequence reagent on an array and not repeating the method over the whole array.

Applicants submit that the Examiner may not appreciate the method to which Applicants have directed this claim. In order to clarify this issue, Applicants have canceled claim 32 and added new claim 35, which is directed to methods in which a plurality of sequencing reagents are used to form a plurality of primer-polymerase complexes and in turn are used to generate a pattern on an array. Applicants direct the Examiner to page 24 lines 15 -19 for support for this amendment.

Response to Rejection of Claims 19, 20, 23 -27 and 31 under 35 U.S.C. § 112, ¶2

The Examiner rejects claims 19, 20, 23 -27 and 31 under 35 U.S.C. § 112, ¶ 2 because they depend either directly or indirectly on canceled claim 1. Applicants have amended these claims to depend either directly or indirectly on claim 4. Consequently, Applicants submit that this rejection should be withdrawn.

Response to Rejection of Claims 19, 20, 23 -27 and 31 under 35 U.S.C. § 102

The Examiner rejects claims 19, 20, 23 -27 and 31 under 35 U.S.C. § 102 as being anticipated by Cantor, reiterating and maintaining the rejection described in the Office Action

dated December 15, 2000. The Examiner notes that this rejection is being maintained because these claims still depend on claim 1.

Applicants have amended these claims to depend either directly or indirectly on claim 4. Thus, for the reasons already provided in Applicants' June 14, 2001 Response, as well as the reasons identified above, that currently pending claim 4 is patentable over Cantor, so too are claims 19, 20, 23 -27 and 31, and this rejection should be withdrawn.

Response to Objections to the Disclosure

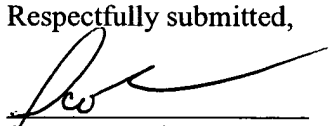
The Examiner objects to certain typographical errors in the disclosure. Applicants have amended the Specification in order to obviate these objections.

CONCLUSION

Based on the foregoing arguments and amendments, Applicants respectfully submit that this application is in condition for allowance. If the Examiner has any questions or concerns regarding this application, he is invited to contact the undersigned attorney.

Applicants submit that no fee is due with this submission other than the fee for the one-month extension of time in which to respond to the outstanding Office Action. However, if any fee is due at this time, the Patent Office is hereby authorized to charge Deposit Account No. 11-0171 for such sum accordingly.

Respectfully submitted,



Scott D. Locke, Esq.
Registration No.: 44,877
Attorney for Applicant

Telephone No. (212) 813-1600

PATENT 13065

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Boyce-Jacino *et al.* Examiner: A. Marschel

Serial No.: 09/097,791 Art Unit: 1631

Filed: June 16, 1998

Title: *"Polymerase Signaling Assay"*

Kalow & Springut LLP
488 Madison Avenue, 19th Floor
New York, New York 10022

October 29, 2002

Commissioner for Patents
Washington, D.C. 20231

MARKED UP CLAIMS PURSUANT TO 37 CFR § 1.121

Sir:

Pursuant to 37 C.F.R. § 1.121, a marked-up copy of the amended claims follows:

IN THE CLAIMS

Please amend claims 4, 13, 19, 20, 23, and 27 to read as follows:

4. (Twice Amended) A method for analyzing a sequence of a template, said method comprising:
   (a) capturing the template with a sequencing reagent to form a captured template, said sequencing reagent comprising:
      i. a capture moiety;
      ii. a spacer region; and
      iii. a primer region, wherein said primer region is adjacent to said spacer region;

Certificate of Mailing Under 37 CFR § 1.8

I hereby declare that on the date provided below, this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231.

10/29/02
October 29, 2002

K Padilla
Kim Padilla

(b) forming a primer-polymerase complex, said primer-polymerase complex comprising said primer region and a polymerase;

(c) scanning the captured template using said primer-polymerase complex for a region of complementarity to said primer region and **forming a duplex**, wherein said region of complementarity to said primer region is not adjacent to a region that is [complementary to] **capable of forming a duplex** with said spacer region;

(d) extending the primer by at least [two] **one** nucleotide **moiety** [moieties] by means of a template-homology dependent extension reaction to form an extended primer; and

(e) detecting said extended primer, wherein detecting said extended primer indicates the presence of one or more regions of complementarity to the primer in the captured template.

13. (Amended) The method of Claim 4, wherein the capture moiety is on a first reagent and the primer region is on a second reagent, **and said first reagent and said second reagent are not attached to one another**.

19. (Amended) The method of Claim **4**, [1] wherein the **at least one** nucleotide **moiety is a** [moieties are] non-chain terminating nucleotide[s] or **an analog of a non-chain terminating** nucleotide [analogues].

20. (Amended) The method of Claim 19, wherein the **at least one** nucleotide **moiety is a** [moieties are] deoxynucleoside triphosphate base[s] or **a** ribonucleoside triphosphate base[s].

23 (Amended) The method of Claim **4** [1], wherein the at least one nucleotide moiety is detectably label.

27 (Amended) The method of Claim **4** [1], wherein the extended primer is detected by change in mass.

For the reasons set forth in the accompanying Response to Non-Final Office Action, Applicants respectfully request entry of these amendments.

Respectfully submitted,

Scott D. Locke, Esq.
Registration No.: 44,877
Attorney for Applicant

Telephone No. (212) 813-1600